REMARKS

Status of the claims

Claims 1-4, 6-7 and 10 are pending. Claims 1-4, 6-7 and 10 are rejected. Claims 1, 3-4 and 7 are amended herein. Claim 10 is canceled. No new matter has been added.

Amendments to the claims

Independent claims 1 and 4 are amended to overcome rejections under 35 U.S.C. 102(e) and 103(b), as discussed *infra*. Claims 3 and 7 are amended to simplify claim language by deleting the term "from". No new matter has been added.

The 35 U.S.C. §102(e) rejection

Claims 1-2, 4-6, and 10 stand rejected under 35 U.S.C. §102(e) as being anticipated by **Jain** *et al.* (U.S. Patent No. 6,010,712). Applicant respectfully traverses these rejections.

The Examiner states that **Jain** *et al.* expressly disclose a method of treating sepsis by administering basic fibroblast growth factor to an animal suffering from said condition (col. 8, ll. 34-35). Applicants submit that **Jain** *et al.* teach a method of treating a

condition involving vascular adhesion of cytotoxic white cells by administering basic fibroblast growth factor to decrease cell surface expression of ICAM-1 or VACM-1 and/or E-selectin on endothelial cells thereby reducing adhesion of cytotoxic white cells to vascular endothelium (Abstract). **Jain's** method purportedly can be used to treat sepsis, inflammation, cancer, and reperfusion injury (col. 8, ll. 31-35). Basically, **Jain** *et al.* teach a method to reduce an immune response, such as inflammation.

Applicants' invention, as recited in amended independent claims 1 and 4, is drawn to methods of treating endotoxic shock or of inhibiting lipopolysaccharide-induced endothelial apoptosis, respectively, by inhibiting ceramide generation from sphingomyelin via administration of basic fibroblast growth factor. Applicants have canceled claim 10.

Applicants submit that endotoxic shock is not sepsis. Enclosed is a recent article by **Reidemann** *et al.* (*The Enigma of Sepsis, J Clin Invest.* 112(4): 460-467 (2003)) that discusses the clinical definition of sepsis and treatments thereof over the last 40 years.

As disclosed in the instant specification and as known in the art, endotoxic shock is induced by lipopolysaccharide present

only in the cell wall of gram negative bacteria. **Riedemann** *et al.* disclose that since the late 1980s, which is prior to the publication of **Jain** *et al.*, sepsis was caused predominantly by gram positive bacteria (pg. 1, first paragraph). Furthermore, **Reidemann** *et al.* disclose that results obtained in lipopolysaccharide infusion animal models often did not mimic the changes observed during sepsis and that anti-inflammatory strategies, e.g., anti-TNF-α and anti-lipopolysaccharide interventions, failed in septic patients. Thus, **Reidemann** *et al.* state that those of ordinary skill in the art concluded that lipopolysaccharide is the agent of endotoxic shock, but not of sepsis and, generally, lipopolysaccharide injection may serve as a model for endotoxic shock but not for sepsis (pg. 3, first 2 paragraphs). Accordingly, a person having ordinary skill in this art could reasonably conclude that endotoxic shock and sepsis are two distinct pathophysiological states.

The instant invention specifically has demonstrated that the agent for the endotoxic shock response, lipopolysaccharide, induces ceramide generation from sphingomyelin which subsequently induces apoptosis in the endothelial microvasculature. The instant application further has demonstrated that basic fibroblast growth factor inhibits ceramide generation in endotoxic

shock. **Riedemann** *et al.* disclosed that, at the time of the instant invention, it was agreed in the art that endotoxic shock is different from sepsis. Thus, **Jain** *et al.* may teach treating sepsis, but not endotoxic shock. Furthermore, **Jain** *et al.* definitely do not teach inhibiting lipopolysaccharide-induced endothelial apoptosis via inhibition of ceramide generation from sphingomyelin.

For a valid §102 rejection, the prior art references must contain each element of the claimed invention. Absent any teachings of treating endotoxic shock or of inhibiting lipopolysaccharide-induced endothelial apoptosis by administering basic fibroblast growth factor and inhibiting ceramide generation from sphingomyelin, **Jain** *et al.* do not anticipate Applicant's claimed invention. Therefore, as this reference is not valid prior art against the instant application under 35 U.S.C. §102 and in view of the preceding amendments and remarks, Applicant respectfully submits that the cited references do not anticipate claims 1-2, 4-6 and 10 under 35 U.S.C. §102. Accordingly, Applicant respectfully requests that the rejection of claims 1-2, 4-6 and 10 under 35 U.S.C. §102(e) be withdrawn.

The 35 U.S.C. §103(a) rejection

Claims 1, 3-4 and 7 stand rejected under 35 U.S.C. §103(a) as being unpatentable over **Jain** *et al.* Applicant respectfully traverses this rejection.

The Examiner maintains that, as independent claims 1 and 4 are anticipated by **Jain** *et al.*, it would be obvious to one of ordinary skill in the art to administer basic fibroblast growth factor to treat sepsis, as taught by **Jain** *et al.*, and to optimize both the dosage and duration of administration because the optimal dosage for a given patient depends upon weight, age and gender and can be determined by one of ordinary skill in the art.

As discussed *supra*, Applicants submit that **Jain** *et al.* do not anticipate amended independent claims 1 and 4. **Jain** *et al.* do not teach treating endotoxic toxic nor inhibiting lipopolysaccharide-induced endothelial apoptosis. Nor is a suggestion found in **Jain** *et al.* to do so. Assuming *arguendo*, one of ordinary skill in the art may make a mental jump that because administering basic fibroblast growth factor decreases cell surface expression of ICAM-1, VCAM and/or E-selectin to reduce adhesion of the cytotoxic white cells to vascular endothelial cells may treat a condition by reducing inflammation, endotoxic shock, therefore, would be treated by basic

fibroblast growth factor, as endotoxic shock has an inflammatory component. However, no reasonable expectation of success is found.

To reiterate, **Jain** *et al.* teach a method of inhibiting adhesion of cytotoxic white cells to endothelium by decreasing expression of certain CAM and selectin molecules to which the cytotoxic white cells adhere via administration of basic fibroblast growth factor. As stated *supra*, this is a method of reducing an inflammatory response. However, **Jain** *et al.* do not demonstrate in any *in vivo* model that basic fibroblast growth factor effects treatment of sepsis or any of the conditions listed.

Reidemann *et al.* disclose that sepsis is not endotoxic shock, that lipopolysaccharide is not an agent for sepsis, that methods of treating lipopolysaccharide-induced endotoxic shock are not successful in sepsis and that most anti-inflammatory strategies for the treatment of sepsis over the last 40 years have failed (pg. 3, last paragraph). Additionally, **Reidemann** *et al.* disclose that the immune system in a septic individual undergoes substantial modifications during sepsis and an anti-inflammatory strategy may not be helpful and even harmful (pg. 4, second paragraph). In view of these disclosures, Applicants strongly maintain that the *in vitro*

results in **Jain** *et al.* do not support even a reasonable expectation of success in treating sepsis *in vivo*, let alone endotoxic shock or a component thereof. Such teaching is found in Applicants' specification.

Lacking all the elements of the instant invention and, given the state of the art at the time of the instant invention as disclosed by **Riedemann** *et al.*, a reasonable expectation of success, **Jain** *et al.* do not render claims 1 and 4 obvious. Claims 3 and 7 depend from claims 1 and 4, respectively, and further limit the dose of basic fibroblast growth factor administered. If independent claims 1 and 4 are neither anticipated by nor obvious over **Jain** *et al.*, then the incorporation of the limits of dependent claims 3 and 7 into claims 1 and 4 does not render the invention obvious.

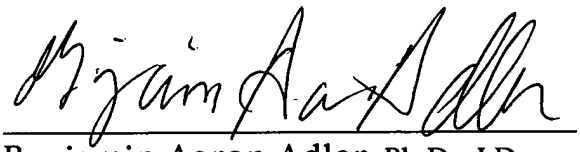
Accordingly, Applicant respectfully requests that the rejection of claims 1, 3-4 and 7 under 35 U.S.C. §103(a) be withdrawn.

This is intended to supplement the response to the Final Office Action mailed June 24, 2003. If any issues remain, the Examiner is respectfully requested to telephone the undersigned attorney of record. Please debit the $385 fee under 37 C.F.R. 1.17(e) to file a Request for Continued Examination or any

additional applicable fees due from Deposit Account 07-1185. As the Examiner has set the period of reply to the Advisory Action to expire six (6) months from the June 24, 2003 mailing date of the Final Office Action, Applicant believes no additional extension fees are due.

Respectfully submitted,

Date: Dec 23, 2003



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